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Exploration of Ferulic Acid and Its Derivatives as Potent Anti-Tyrosinase: A Systematic Review

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Abstract

Tyrosinase is an enzyme that catalyzes melanin biosynthesis. Recently, it has become a popular target for developing cosmetics as a skin lightening or skin whitening agent, an anti-aging agent, an anti-wrinkle agent, and other therapeutics for skin disorders. Based on the previous reports, many compounds have been developed and designed to be tyrosinase inhibitors, including ferulic acid and cinnamic acid derivatives. However, until now, the use of these compounds in commercial cosmetic products has been limited. It may be due to chemical instability, lipophilicity, and poor efficacy. In this review, we assessed research studies to discuss the structure-activity of ferulic acid and its derivatives, which can contribute to their better efficacy as anti-tyrosinases. Either ferulic acid as a single compound or its hybridization with other cinnamic acid derivatives proved beneficial in designing tyrosinase inhibitors as active functional groups. The structure-activity of the phenyl ring's substituent improved inhibitory effects on monophenolase activity, especially the halogen substituent. In addition, the alkyl chain length and other functional groups linked, such as amide and acetyl groups, could alter the inhibitory properties, including hydrophobicity, to produce a more stable complex ligand-receptor.

Keywords: Ferulic acid; Ferulic acid derivatives; Anti-tyrosinase; Anti melanogenesis.

1. Introduction

Melanin biosynthesis (melanogenesis) is a physiological response of human skin to absorb ultraviolet (UV) radiation. Exposure to UV radiation on the skin induces reactive oxygen species (ROS) production. The imbalance between excessive free radicals and ROS production leads to oxidative stress. Free radicals and ROS are very reactive, resulting in overexpression melanogenesis [1]. It can lead to skin darkening and abnormal hyperpigmentation that causes many dermatological problems, such as melasma, skin cancer, senile lentigines, and freckles [2]. The biosynthesis of melanin begins with the hydroxylation of L-tyrosine to L-dihydroxyphenylalanine (DOPA) and then DOPA oxidation to dopaquinone. The reactions are specifically catalyzed and regulated by melanocyte tyrosinase [3]. Therefore, the most common strategy to prevent melanin biosynthetics is inhibiting tyrosinase activity.

Currently, several cosmetic products or skin-lightening agents on the market are developed as tyrosinase inhibitors to control tyrosinase enzyme activity. They are hydroquinone, kojic acid, ascorbic acid, azelaic acid, and arbutin [4]. However, their use is limited in medicine and cosmetic products because of their chemical instability [1] and undesirable side effects such as dermatitis, skin cancer, cytotoxicity, and neurodegenerative disease [5]. Thus, developing new tyrosinase inhibitors with optimal and stable physicochemical properties and excellent safety and efficacy is still an enormous challenge.

There are many reports that polyphenols have shown a potential inhibitory effect on tyrosinase, such as cinnamic acid derivatives and some natural extracts rich in ferulic acid. Ferulic acid is one of the hydroxycinnamic acids, the cinnamic acid derivatives, present in the plant cell wall and known for its potent antioxidant properties with low toxicity. It possesses many biological activities (antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and anticancer) [6].

Ferulic acid can donate electrons and form a radical

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phenolic ring known as an excellent antioxidant to treat diseases associated with free radicals [7]. Its chemical structure has a high-level conjugated unsaturation bond, making it a potent UV absorber [8]. It can not only abstract free radicals but also enhance the scavenging free radical activity of enzymes and impede the issue of radicals catalyzed by the enzymes [9].

The clinical usage of ferulic acid is still up for discussion due to its low bioavailability, although it exhibits minimal toxicity and various biological activity. Additionally, ferulic acid has poor stability in various solvent systems limiting its applicability in the cosmetic, pharmaceutical, and food industries. However, ferulic acid is a highly reactive substance that could create a variety of derivatives [10].

Many studies have been done to investigate the tyrosinase inhibitor activity of ferulic acid and its derivatives to date. However, studies have yet to systematically compare the results of different studies and the structure-activity relationship. In the present study, the author systematically selected records on this subject, compared the structure of ferulic acid derivatives with their biological activity, and made computational predictions of the reviewed compounds' physicochemical properties that could be good anti-tyrosinases.

2. Methods

Searching many kinds of literature was done by following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram [11]. The database used includes Science Direct and PubMed. A systematic search was performed using the search terms: “Synthesis”, “ferulic acid”, “ferulic acid Derivatives”, “anti-tyrosinase”, “anti melanogenesis”, “tyrosinase inhibitor”, and “melanogenesis inhibitor”, using the Boolean operator.

The following are the criteria for article inclusion: (1) Full text or the original research articles should be accessible; (2) articles should be published in English; and (3) articles should explain ferulic acid or the synthesis of its derivatives accompanied in vitro experiments of tyrosinase inhibitory activity, simultaneously. Meanwhile, the exclusion criteria were: (1) Articles not written in English; (2) non-related studies; (3) review articles; (4) duplicate articles; and (5) articles not available as full text.

The writers performed data extraction from the literature independently with a focus on (1) in vitro studies for ferulic acid or its derivatives and (2) synthesis with followed in vitro studies. Therefore, studies on natural sources and drug delivery systems were taken out. After removing the duplicate, we assessed the identified studies based on the title and abstract according to the inclusion and exclusion criteria.

3. Result and Discussion

A total of 820 potentially relevant published articles were found through database searching. After removing eight duplicate articles and 443 review articles, 369 articles were screened based on inclusion and exclusion criteria, and finally, collected 14 articles in full text as shown in **Fig. 1**.

Considering the active compound in the study, 12 of 14 articles performed the study of tyrosinase inhibitory use of ferulic acid (**Table 1**) or its derivatives (**Table 2**) as a single compound. While the remaining two reported the anti-tyrosinase activity of a combination of ferulic acid with other cinnamic acid derivatives (**Table 3**). The studies showed that combining ferulic acid with other inhibitors has a synergetic effect.

There are two basic approaches to assessing tyrosinase inhibitors in the literature. The first and most used technique employs a commercially available mushroom tyrosinase. The second is a cellular assay, measuring the intracellular accumulation of melanin or the rate of substrate transformation [12]. Some of the articles reviewed here are those that conduct both tests.

Table 1. Study of Anti-Tyrosinase of ferulic acid as a single compound

Method of anti-tyrosinase test	Result of ferulic acid	Ref.
In vitro using L-DOPA as substrate	IC_{30}: > 30 μM	[13]
In vitro using L-DOPA as substrate	% inhibition at 51.5 μM: 98.2	[14]
In vitro using B16F10 cell	% Melanin content at 0,314 mM: 27.14	
In vitro using L-DOPA as substrate	IC_{50}: 243 ± 6.2 μM	[15]

3.1. Ferulic Acid

Ferulic acid ([E]-3-[4-hydroxy-3-methoxy-phenyl] prop-2-enoic acid), as a phenolic acid substance, is one of the cinnamic acid derivatives, namely hydroxycinnamic acid. It is widely distributed in the plant, mainly in whole grains, wheat, cereal seeds, rye, oats, and barley [6].

It is one of the metabolites of lignin production. Beginning with phenylalanine and tyrosinase (two aromatic amino acids), which are biosynthesized through the shikimate route [16].

In 1866, Hlaziwetz and Barrth discovered protocatechuic acid and resorcinol from the

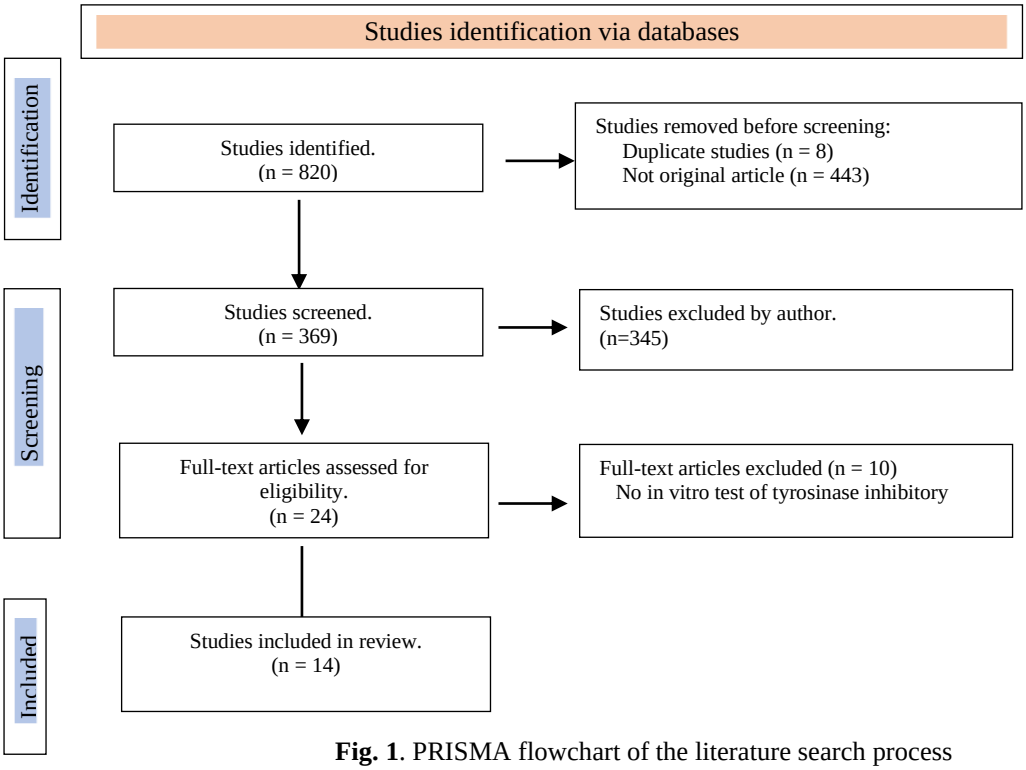

Fig. 1. PRISMA flowchart of the literature search process

commercial resin of *Ferula foetida*. When they added. divalent lead to an alcohol resin solution, they simultaneously obtained a pale-yellow precipitate. They reconstituted the free acid after washing the precipitated lead salt with alcohol. Elemental analysis revealed that it is composed of $C_{10}H_{10}O_4$. It is called ferulic acid [17].

Furthermore, ferulic acid can be obtained by organic synthesis to improve yield and reduce preparation times. One method of ferulic acid synthesis is the condensation reaction of Knoevenagel-Doebner vanillin with malonic acid using piperidine [18] or proline [19] as a catalyst and microwave-assisted reaction [19-21]

Ferulic acid has a relative molecular weight of 194 g/mol, a melting point of 174ºC, poor stability in an aqueous solution, and is soluble in hot water, methanol, ethanol, and acetone [22]. Ferulic acid is relatively hydrophilic, with an apparent partition coefficient of 0.3753 at pH 3 and 0.489 at pH 10. It is hygroscopic by absorbing moisture at a relative humidity of over 76% at 25ºC [23]. The molecule has an unsaturated side chain; they are the *trans* (white crystalline form) and *cis* isomers (yellow oily liquid), as depicted in **Fig. 2.** It is usually found as mono- or oligosaccharides, proteins, lipids, and specific polysaccharides [18, 24-25].

Ferulic acid consists of a benzene ring (phenyl), an ethylenic link, methoxy, hydroxy, and carboxy groups. The methoxy and phenyl hydroxyl groups significantly improve their electrophilic reactivity.

Due to its structural properties, this active substance is an excellent substrate for synthesizing derivatives such as ester, ether, amide, anhydride, acyl chloride, and polymers [10]. The excellent antioxidant capability of ferulic acid is strongly related to the presence of electron-donating groups attached to the benzene ring, such as methoxy and hydroxyl [26]. A hydroxy group at the ortho position to a methoxy group causes the phenoxy radical to be more stable and increases the antioxidant effectiveness of ferulic acid. Combining the phenolic ring and unsaturated side chain causes a resonance-stabilized phenoxy radical. The resonance stabilization explains how ferulic acid has an effective antioxidant capacity [22]. It might provide more sites for free radicals to attack and prevent them from destroying the cell membrane [27]. In contrast, electron-withdrawing groups like carboxylate, aldehyde, and ester should have the opposite effect. A decrease in ferulic acid's antioxidant/ant-radical activity was observed upon acetylation [26].

Ferulic acid has a high conjugated unsaturation level, making it a potent UV absorber. It absorbs

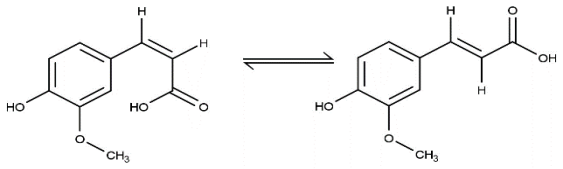

Fig. 2. Structure of cis- and trans- ferulic acid *Source*: Zdunska et al. (2018) has been modified

Table 2. Study of Anti-Tyrosinase of Ferulic Acid Derivatives

Series of compound	Anti-tyrosinase test method (substrate)	Number structure	Result of tyrosinase inhibition test	Main finding	Ref.
N-hydroxycinnamoyl phenyl alkyl amides	In vitro (L-DOPA)	1	% inhibition at 100 μM: 19 ± 9	Modifying the substituent and the side chain length of the phenyl ring alters the inhibitory activities.	[12]
		2	% inhibition at 100 μM: 49 ± 4		
		3	% inhibition at 100 μM: 62 ± 2		
		4	% inhibition at 100 μM: 25 ± 5		
Cinnamoyl amides with amino acid ester	In vitro (L-DOPA)	5	IC_{50}: 0.185 ± 0.005 μM	The substituents at the styrene groups and the extension of hydrocarbon chains at the amino acid esters impacted the inhibitory effects.	[29]
Hydroxycinnamoyl phenylalanyl/prolyl hydroxamic acid derivatives	In vitro (L-DOPA)	6	% inhibition at 100 μM: 40	The methoxy group at a para position to the hydroxyl group may have caused steric hindrance when arriving at tyrosinase' active site.	[30]
		7	% inhibition at 100 μM: 25		
N-hydroxycinnamoyl amides of fluorinated amino acids	In vitro (L-tyrosine)	8,9	no significant	Fluorine moiety can increase the radical scavenging activity. It does not apply to the anti-tyrosinase activity	[31]
Hydroxycinnamic acid linked to benzyl piperazines	In vitro (L-tyrosine)	10	IC_{50}: 66.5 mM	p-fluoro- or p-methoxybenzyl piperazine in the amide make better inhibition properties	[32]
		11	IC_{50}: 61.1 mM		
1-(4-hydroxy-3-methoxyphenyl) pent-1-en-3-one (HMPPEO)	In vitro (L-tyrosine and L-DOPA)	12	% inhibition at 10 mM: 40 (L-tyrosine as substrate) and 50 (L-DOPA as substrate)	HMMPEO has a similar structure to ferulic acid and dehydrozingerone. It had an equal ability to scavenge free radicals but a higher activity as a tyrosinase inhibitor.	[33]
N-hydroxycinnamoyl amide derivatives	In vitro (L-tyrosine)	13, 14, 15, 16,17, 18, 19	IC_{50}: < 0.18 μM (18 is the most active)	Acetyl groups are more effective than amide	[34]
Dimeric cinnamoyl amide analogs	In vitro (L-tyrosine)	20	IC_{50}: > 150 μM	Three of the diamide-link chains possessed a higher activity as a tyrosinase inhibitor and melanin production than two or four of the diamide-link chains.	[35]
		21	IC_{50}: 98.3 ± 2.1 μM		
		22	IC_{50}: 108.4 ± 2.5 μM		
	In vitro using B16F1 cell	20	IC_{50}: > 150 μM		
		21	IC_{50}: 65.2 ± 1.9 μM		
		22	IC_{50}: 88.4 ± 3.3 μM		
	melanin content	20	IC_{50}: > 150 μM		
		21	IC_{50}: 122.8 ± 1.4 μM		
		22	IC_{50}: > 150 μM		
Cinnamyl-phenol ester analogs	In vitro (L-DOPA)	23	IC_{50}: 13.98 ± 5.44 μM	Phenolic hydroxyl groups could increase anti-tyrosinase properties	[36]
		24	IC50: 15.16 ± 4.76 μM		
	In vitro using B16F1 cell	23	Inhibition ratio values of 23.83%		
		24	moderate inhibition		

Ferulic acid has a high conjugated unsaturation level, making it a potent UV absorber. It absorbs radiation and generates phenoxy radicals that then transform into cis-trans isomers. Ferulic acid can reduce the quantity of UV radiation and prevent UV radiation from oxidizing other light-sensitive chemicals [28]

Table 2. Study of Anti-Tyrosinase of Combination Ferulic acid with other Cinnamic Acid Derivatives

Study design	Study topic	Main Finding	Ref.
Anti-tyrosinase activity. Substrate: L-DOPA	The combined effect and inhibition mechanism of 4-hydroxycinnamic acid and ferulic acid to tyrosinase activity.	Combining ferulic acid and caffeic acid as tyrosinase inhibitors was more efficient than only caffeic acid or ferulic acid (inhibition rate of 90.44%, 12.15%, and 22.17%, respectively).	[37]
Anti-tyrosinase activity: Substrate: L-DOPA	Action mechanism of five individual polyphenols (quercetin, gallic acid, ferulic acid, isorhamnetin, 4-hydroxycinnamic acid) as a tyrosinase inhibitor.	A combination of ferulic acid, cinnamic acid, and quercetin (at a concentration each substance is 5 mM) exhibited the highest inhibition ability (Ki = 0.239 mM) and was most stable because of having a spontaneous binding process with a hydrophobic effect.	[38]

3.2. Melanin Synthetic Pathway

Tyrosinase is a copper-containing metalloenzyme having an obligation to the formation of melanin or melanogenesis through the process of oxidation and polymerization of the common precursor L-tyrosine or L-DOPA. The enzyme is also called polyphenol oxidase [39-40].

Melanin is a pigment that functions in coloring hair, eyes, and skin. It is obtained through the process of melanogenesis that occurs in melanocytes. The reaction mechanism of melanin formation involves two distinct reactions in melanin synthesis. Melanin consists of eumelanin containing dark pigments and phenomelanin with light sulfate pigments obtained from the fusion of cysteine precursors [41].

Genetics and ethnicity play a role in the synthesis of melanin by melanocytes, which is also impacted by several intrinsic and extrinsic variables. Intrinsic variables include molecules secreted by cells around melanocytes, such as endocrine cells, inflammatory cells, fibroblasts, and keratinocytes. Extrinsic variables include ultraviolet radiation and various health products or cosmetics that affect the occurrence of melanogenesis [41-42].

The mechanism of melanin synthesis is initiated by tyrosinase's enzymatic activity. Tyrosinase plays a role in two catalytic cycle activities: the activity of monophenolase and diphenolase. The activity of monophenolase is tyrosinase hydroxylation of monophenol (e.g., L-tyrosine) into o-diphenol (e.g., L-DOPA) and subsequent activity of diphenolase, i.e., tyrosinase oxidation of o-diphenol into o-quinone (o-dopaquinone) [39].

O-dopaquinone has a high reactivity, so it can easily experience Michael's addition reactions at 1,6- and 1,4- with nucleophiles such as thiol and amino acids [43]. It explains why o-dopaquinone plays a crucial function in the chemical regulation of melanogenesis. O-dopaquinone undertakes cyclization of its amine group to be cyclo-dopa (or leucodopachrome) without thiol compounds [44]. Thiol and L-cysteine transform dopaquinone into cysteinyldopa isomers, which undergo oxidation to form quinone. The quinone's cyclization and rearrangement reactions produce the benzothiazine intermediates to be pheomelanin by oxidation [45].

Cyclo-dopa (or leucodopachrome) will be rapidly oxidized due to the presence of a reduction-oxidation reaction with o-dopaquinone, producing dopachrome and L-dopa. Dopachrome will gradually and spontaneously be converted mostly to 5,6-dihydroxyindole (DHI) through the rearrangement of decarboxylation and slightly into 5,6-dihydroxyindole-2-caboxylic acid (DHICA) [44], [46]. Oxidative polymerization of DHI and DHICA generates eumelanin [43].

3.3. Inhibition of Tyrosinase Activity

Melanin synthesis can be inhibited by three mechanisms: reduction of tyrosinase activity, decreased levels of Microphthalmia-associated Transcription Factor (MITF), and absorption of UV radiation. However, inhibiting tyrosinase activity is the most typical approach to do so [5]. The interaction of inhibitor and tyrosinase is a constantly changing and reversible reaction. It occurs when the quantity of the inhibitor increases and the tyrosinase activity decreases, but it is not entirely inactivated [47].

There are four types of inhibitory mechanisms. They are competitive, uncompetitive, mixed type (competitive/uncompetitive), and non-competitive inhibitors [39]. 1) Competitive enzyme inhibitors bind to the enzyme's active site of free enzymes and prevent the substrate from binding. Therefore, it competed with the other substrates, like L-tyrosine and L-dopa. 2) Uncompetitive enzyme inhibitors only attach to complexes of enzyme-substrate. It may interact with amino acid residues to change the conformation of tyrosinase. 3) Mixed-type (competitive or uncompetitive) inhibitors interact with both free enzymes and enzyme-substrate complexes. And 4) non-competitive inhibitors

interact with free enzymes and enzyme-substrate complexes with the same equilibrium constant [47].

According to studies by Rangkadilok et al. (2007) [48] the antioxidant activity of phenolics increases with the presence of several hydroxyl groups. Tyrosinase activity may be inhibited by the hydroxyl groups of the phenolic, which may create a hydrogen bond with the enzyme's amino acid residue and decrease its activity. Some tyrosinase inhibitors work by attaching their hydroxyl groups to the tyrosinase's active site, which causes steric hindrance or altered conformation [2]. Molecules with the capacity to decrease oxidative stress would be capable of controlling melanogenesis by reducing tyrosinase activity and melanin synthesis [49].

There were a few known compounds with mechanisms such as tyrosinase inhibitors, namely kojic acid and arbutin. Kojic acid acts as an excellent chelator of transition Cu^{2+}, a scavenger of free radicals, and a blocker for the polymerization of dihydroxy indole. However, it was unstable to light and high temperatures, skin's poor absorption, and for long-term use induced skin cancer [38]. In contrast, arbutin produces hydroquinone in long-term storage [5].

Ferulic acid displays the perfect structure as a competitive inhibitor of tyrosinase, which catalyzes processes in the melanin biosynthetic cycle by blocking L-dopa from incorporating the active sites (**Fig. 3**), changing the secondary structures of the enzyme, and inducing instability and unfolding of the protein [7]. It was discovered to be a more potent melanin inhibitor than caffeic acid by directly binding to tyrosinase [14].

3.4. Derivatives of Ferulic Acid and Their Activity as Anti-Tyrosinase

Because ferulic acid has promising potential,

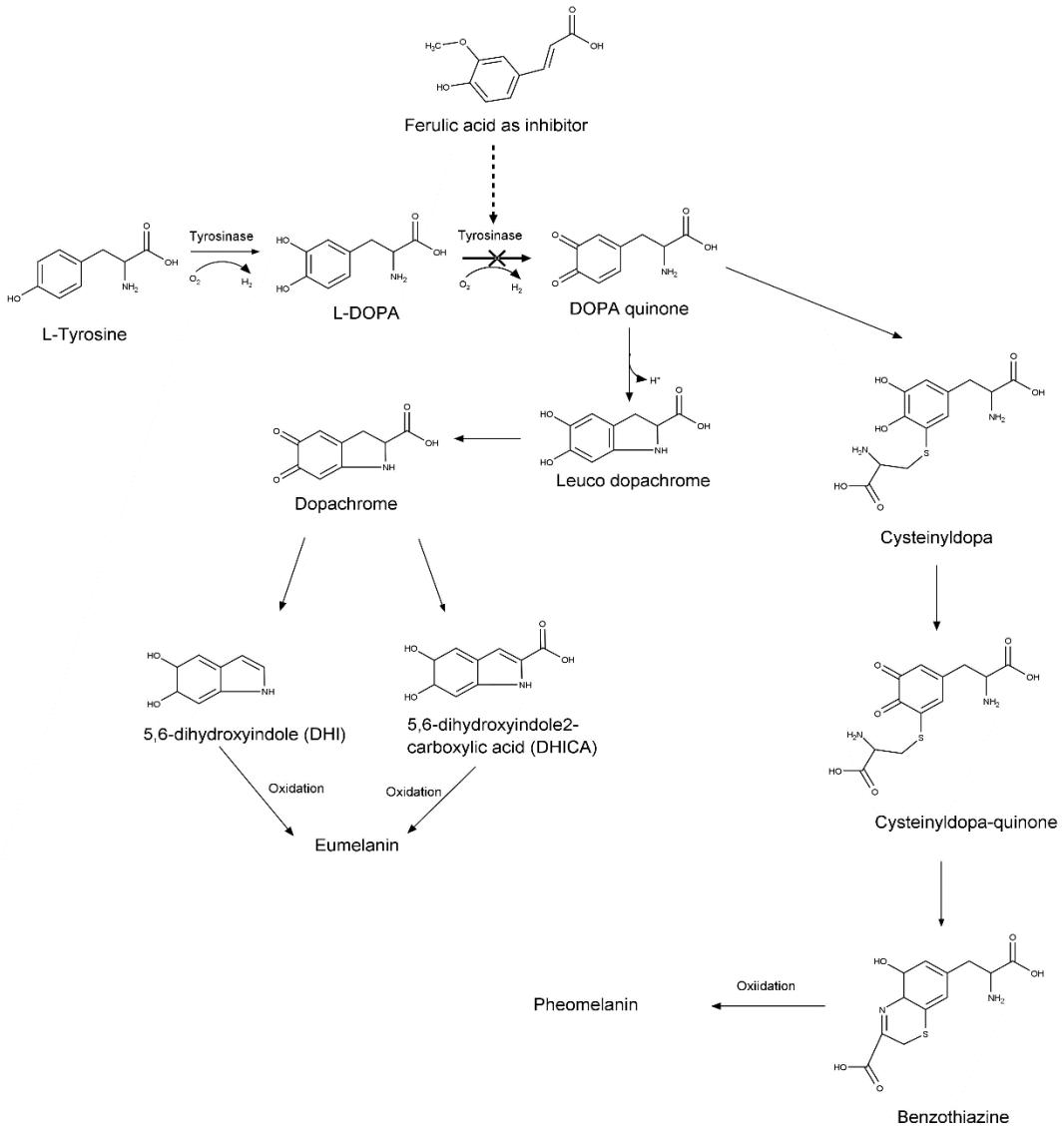

Fig. 3. Scheme of Melanin Biosynthesis *Suorce*: Samaneh et al. (2019) has been modified.

numerous research teams have investigated it based on its structural principles. This section summarizes these compounds and their biological function as anti-tyrosinase.

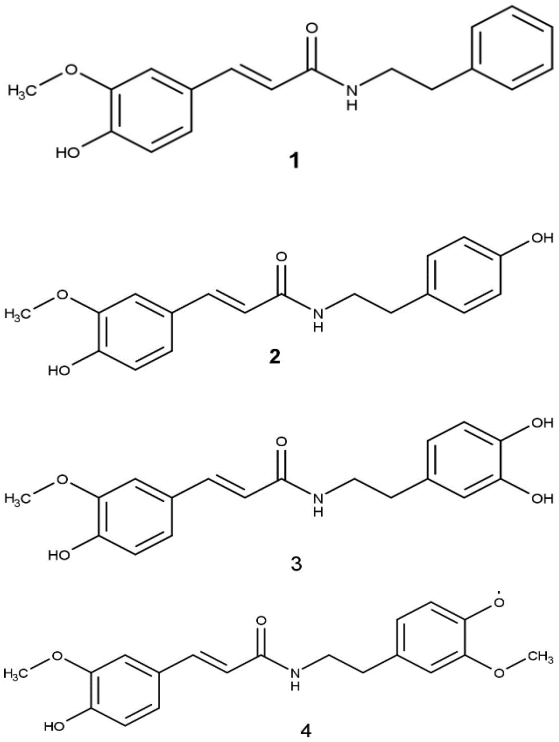

Fig. 4. Structure of ferulic acid derivative reported by Okombi et al.

Okombi et al. (2006)[12] evaluated several amides that were prepared by reacting p-hydroxycinnamic acid derivatives (including ferulic acid) with phenyl alkylamines, against the tyrosinase enzyme. Based on the structure-activity relationship study, amides found by reacting tyramine with dihydrocaffeic acid, caffeic acid, and dihydro-p-hydroxycinnamic acid displayed higher activity than ferulic acid, caffeic acid, and dihydro-p-hydroxycinnamic acid, which are known having potent antioxidant activity. Furthermore, the anti-tyrosinase activity of ferulic acid derivatives (% inhibition at 100 µM of compounds **1**,**2**,**3** and **4** (**Fig. 4**) is 19 ± 9, 49 ± 9, 62 ± 2, and 25 ± 5 respectively) were more effective than that of ferulic acid (% inhibition at 100 µM is 12 ± 2). It demonstrates the significance of the amide linkage to activity. The inhibitory characteristics of these compounds are affected by changes in the arrangement of substituents and the length of the chain that separates the phenyl rings from the amide bond.

A similar case was performed by Fan et al. (2012) [29], who synthesized nine cinnamoyl amides with amino acid ester (CAAE) from a combination of the cinnamic acid derivatives. The result of the experiment is ethyl N-[3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]-L-phenylalanic ester (compound **5**), which is the conjunction of ferulic acid with amino acid ester, provides the most potent inhibitory activity (IC_{50} 0.18 µM). Based on the Lineweaver-Burk analysis, the inhibitory mechanism of compound **5** (**Fig. 5**) is a mixed-type inhibitor, where the affinity of the inhibitor for the free enzyme is more potent than that for the enzyme-substrate complex. The side chain at the amino acid ester may contribute to increasing the hydrophobic interactions in forming a stable chelation complex and preventing accessibility of the substrate to the active site [50]. Then, it proves that the extension of alkyl chains at the amino acid esters impacts the inhibitory effect.

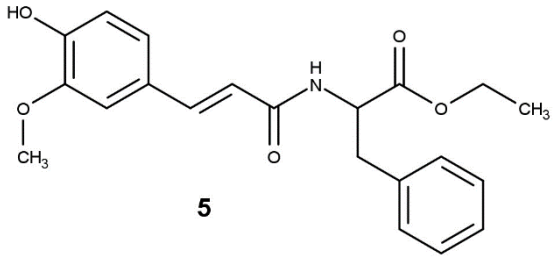

Fig. 5. Molecule of CAAE synthesized by Qian Fan et al.

In research by Kwak et al. (2013) [30], caffeoyl-phenylalanyl-hydroxamic acid (CA-Phe-NHOH) has significantly higher tyrosinase inhibitory activity than ferulic acid and its derivatives (compounds **6** and **7,** shown in **Fig. 6**). The presence of an OCH_3 group at

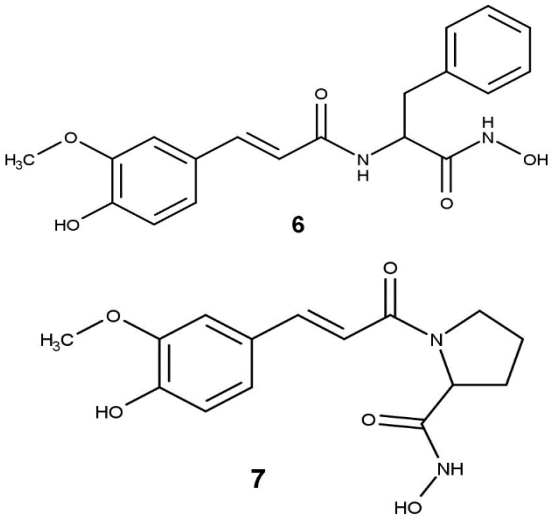

Fig. 6. Derivates of ferulic acid modified by Kwak et al.

a para position to OH group in ferulic acid may have presented steric hindrance when arriving at the tyrosinase' active site. Many studies have revealed that replacing methoxylation in ferulic acid with hydroxylation of caffeic acid gives more efficient activity because the 3,4-hydroxyphenyl ring on caffeic acid is like the natural substrate L-dopa. However, ferulic acid is believed to be more active than p-coumaric acid because the electron-donating methoxy group enhanced the stability of aryloxy radical by electron delocalization after the hydroxyl group donated hydrogen [50].

After that, the effect of the isosteric exchange of hydrogen with fluorine in amino acids against inhibitor capability was investigated by Chockova et al. (2013) [31] in a series of N-hydroxycinnamoyl amides. The amides that react with derivatives of hydroxycinnamoyl are phenylalanine and tryptophan. The modification results show that the derivative of sinapic acid is the most potent inhibitor of dopachrome formation. While ferulic acid derivatives, either FA-Trp 6-(F)-OMe (**8**) or FA-Phe (3-F)-OMe (**9**) as illustrated in **Fig. 7**, showed no significant difference with the parent substance. It was evident that tyrosinase inhibiting activity was not considerably affected by the presence of a fluorine atom at the C-3 or C-6 position in the aromatic ring. The inhibitor tyrosinase capability of the tested amides showed no significant difference with the

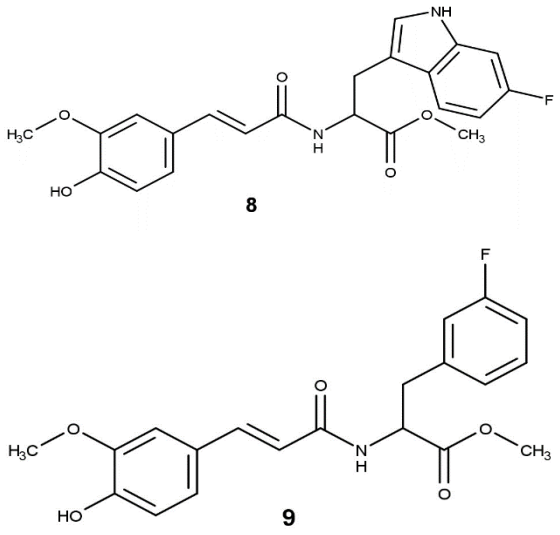

Fig. 7. FA-Trp 6-(F)-OMe and FA-Phe (3-F)-OMe reported by Chochkova et al.

parent substance.

The other experiment was conducted by Chen et al. (2021) [15]. They explored cinnamic acid and its derivatives against the tyrosinase enzyme. The tyrosinase enzyme has two independent binding sites in the catalytic center. They are for the binding of monophenols (monophenolase activity), and the other is for the binding of diphenol (diphenolase activity) [50]. The results of Chen's study found that the phenyl ring's substituents enhanced the inhibition of monophenolase and reduced the inhibition of diphenolase. Halogen substituents enhanced the inhibitory activity of monophenolase. The more electronegative the greater the effect on its inhibitory activity (F > Cl > Br). Based on the experimental study mentioned above, ferulic acid (IC_{50}: 243 ± 6.2 µM) is less effective than trans-3,4-difluoro cinnamic acid (IC_{50}: 68.6 ± 6.2 µM).

The Romagnoli et al. (2022) [51] trial found the same result—a novel series of cinnamic acid derivatives linked to aryl piperazines. Based on the result of the docking test, the piperazine ring does not play a crucial role in binding. However, the modification of the presence of halogen atoms (F or Cl) or a methoxy group on the phenyl at N-4 of the piperazine ring combined with electron-withdrawing (Cl and NO_2) or electron-releasing (amino, methoxy, 3,4-methylenedioxy, or benzyloxy) groups on the phenyl of the cinnamoyl moiety exhibited the most potent tyrosinase inhibitory effect.

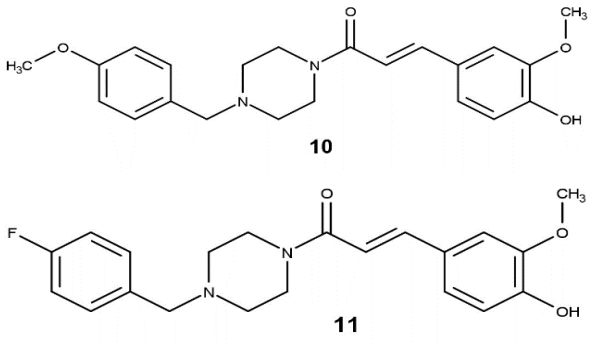

Fig. 8. Derivatives of Ferulic acid designed by Gu et al.

The other study about the combination with piperazine was conducted by Gur et al. (2019) [32] They tried to combine benzyl piperazine amide with hydroxycinnamic acid (such as ferulic acid, caffeic acid, and p-coumaric acid). Among the synthesized compounds, the derivatives of ferulic acid to p-methoxybenzyl and p-fluoro piperazine (compounds **10** and **11,** shown in **Fig. 8**) in the amide exhibited higher inhibition (IC_{50} values of 66.5 and 61.1 mM, respectively). The combination balances the structure to create hydrophobic contact with the active site. Notably, the presence and position of hydroxyl and methoxy on the phenyl ring were essential to affect the inhibitory activity. However, too much hydroxy or methoxy may steer to the loss of inhibitory activity because of electrostatic repulsion and steric hindrance effects [50].

The design and synthesis of derivatives of ferulic acid in **Fig. 9** were carried out by Bai et al. (2021) [33]. His basic idea is that ferulic acid rapidly degrades into numerous derivatives by

decarboxylation and narrow solubility in oils and solvents, which results in a change in product color and a depletion in product efficacy [52]. As a result, it is imperative to obtain an antioxidant with a comparable structure but more lipophilic than

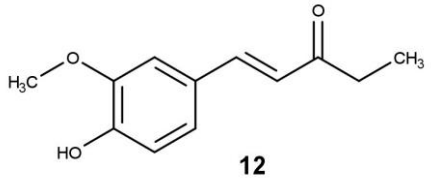

Fig. 9. Structure of HMPPEO designed by Bai et al.

carboxyl. 1-(4-Hydroxy-3-methoxyphenyl) pent-1-en-3-one (HMPPEO), the analog of ferulic acid, has been prepared. The structure of HMPPEO is unique, with the hydrophobic ethyl and methyl on each side of the carbonyl group. It is indicated to have better oil solubility than ferulic acid.

Using L-DOPA as the substrate, the IC_{50} of HMPPEO can be achieved at 10 mM. At the same concentration of ferulic acid, the inhibitory efficiencies only reach less than 40%. It reveals that HMPPEO is more effectively inhibiting than ferulic acid. These findings suggest that HMPPEO could be a promising skin-lightening ingredient in cosmetics 33.

Besides that, Wang et al. (2019) [34] synthesized twelve N-hydroxycinnamoyl amide derivatives (**Fig. 10**) by using raw materials: L-amino acid ethyl ester hydrochloride and cinnamic acid (caffeic acid, ferulic acid, and acetyl ferulic acid), to be evaluated as antioxidants anti-tyrosinase. The result showed that compound **15**, (E)-*N*-(feruloyl acid)-L-phenylalanine ethyl ester, synthesized from ferulic acid had the highest anti-tyrosinase activity (IC_{50} < 0.18 µM).

The sequence of the rate of anti-tyrosinase activity of *N*-feruloyl amide derivatives was as follows: **18** > **17** > **16** > **13** > **15** > **19** > **14**, which correlated to the alkyl chain's structure [35]. The result aligns with the previous report that the increase in tyrosinase inhibitors' hydrocarbon chain length enhances the inhibitory effect [29].

Ha et al. (2018) [35] tried different aspects to enhance tyrosinase inhibition activity by reacting dimeric cinnamoyl amide analogs (DCA) with a

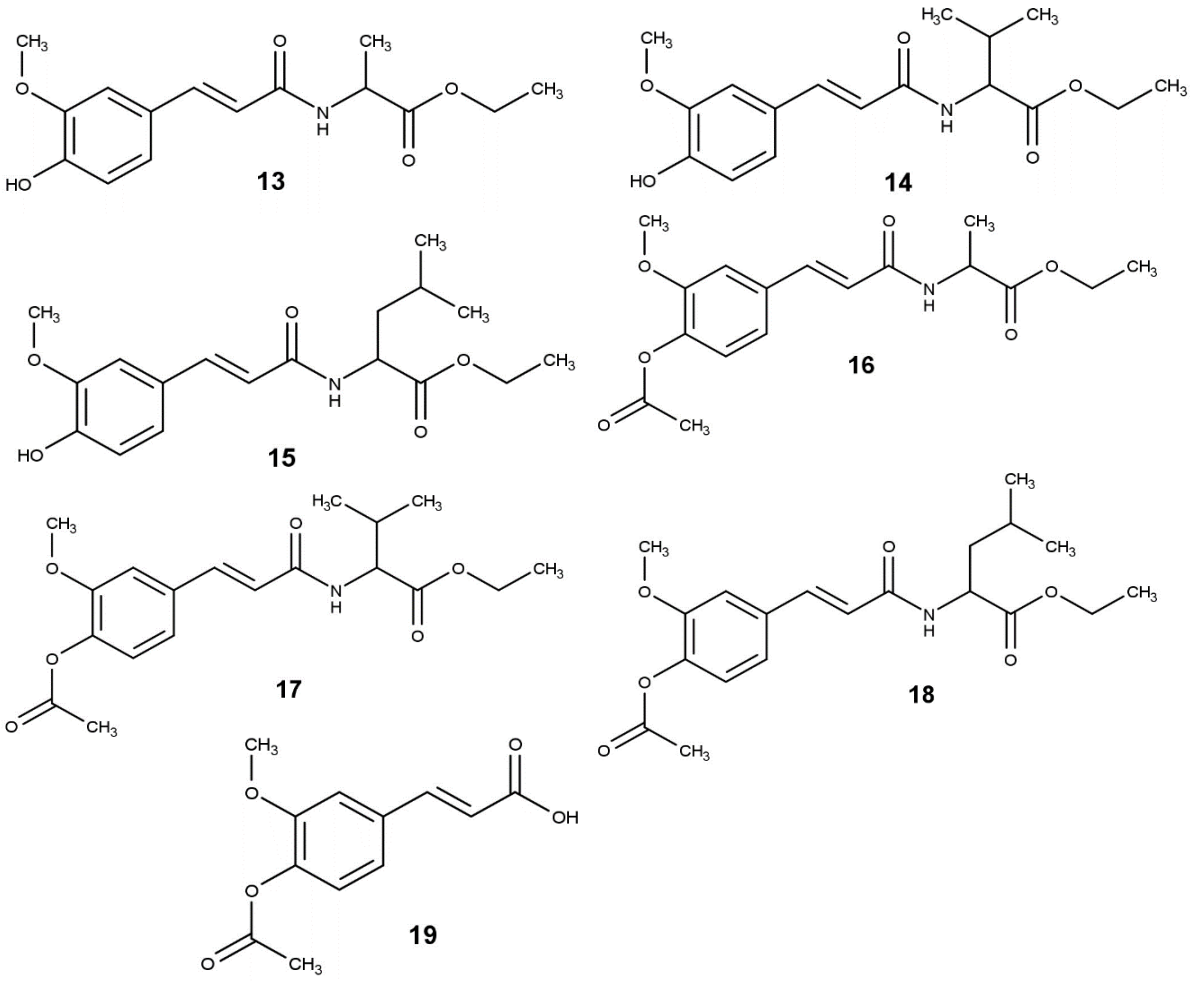

Fig. 10. N-hydroxycinnamoyl amide derivatives of ferulic acid explored by Wang et al.

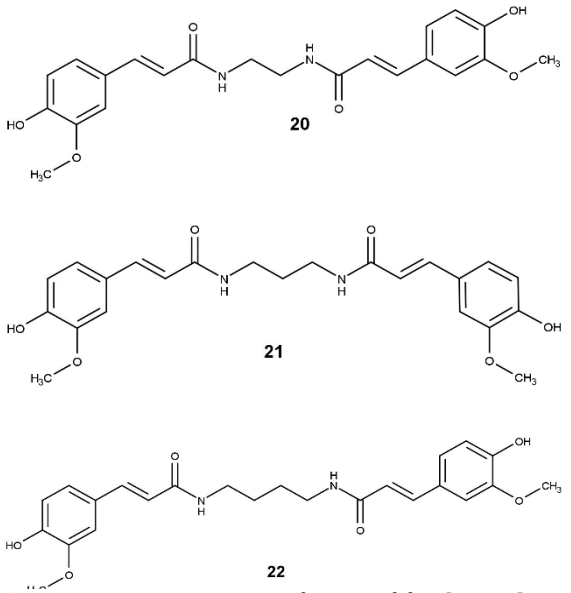

Fig. 11. Pattern Structures of DCA of ferulic acid modified by Ha et al.

diaminoethyl group. DCAs contained different diamide-link chain lengths and OH groups at various positions. As for ferulic acid derivatives produced, they are N, N-diferuloyl-1,2-diaminoethane (**20**), N, N-diferuloyl-1,3-diaminopropane (**21**), and N, N-diferuloyl-1,4-diaminobutane (**22**) as depicted in **Fig. 11**. The experimental study showed that DCAs with three diamide link chains possessed a higher anti-tyrosinase activity and production of melanin than DCAs with two or four diamide link chains. Example: the IC_{50} (μM) value of tyrosinase inhibitory activity is more than 150; 65.2 ± 1.9 and 88.4 ± 3.3; and melanin production is more than 150; 122.8 ± 1.4 and more than 150 for compounds **20**, **21,** and **22**, respectively. Besides that, the position of OCH_3 and/or OH groups is a significant factor in creating the best structure with hydrophobic properties to interact with the active site of tyrosinase. Based on the hydrophobic properties of DCAs by calculating the Log P value, it was found that the Log P higher than 1.5 contributed to increased accessibility to tyrosinases' active site in melanocytes [35].

The other studies regarding some cinnamoyl ester analogs synthesized from cinnamic acid (CA) and phenol compounds were carried out by Tang et al. (2021) [36]. The produced derivatives of ferulic acid are (E)-3-(2-acetyl-5-methoxyphenoxy)propyl-3-(4-hydroxy-3-methoxyphenyl) acrylate (**23**) and (E)-3-(3-acetyl-4-hydroxyphenoxy)propyl-3-(4-hydroxy-3-methoxyphenyl) acrylate (**24**) as shown in **Fig. 12** which have more potent anti-tyrosinase activity (IC_{50} = 13.98 μM and 15.16 μM, respectively), than the positive control, kojic acid (IC_{50} = 30.83 μM). In addition to the alkyl chain length, the number of OH phenolics also helped improve the anti-tyrosinase activity. The IC_{50} decreases, or the inhibitory activity increases with increasing numbers of OH phenolic groups. Replacing the corresponding OH phenolic group reduced the effect dramatically [53]. The result displayed inhibitory activity for di-phenols > mono-phenols > non-phenol compounds.

Based on molecular docking analyses, compound **24** interacted with the active site through a hydrogen bond, which easily formed H-bond with electrophilic O in the ester group and phenolic hydroxyl group [36].

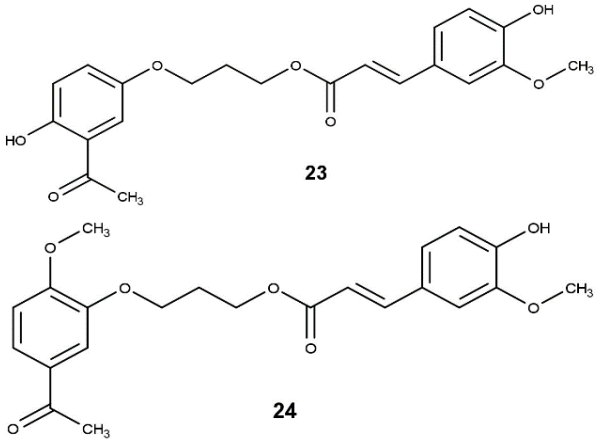

Fig. 12. Cynnamyl-phenol derivatives of ferulic acid synthesized by Tang et al.

Then, the other study was performed by Maruyama et al. (2018) [14]. They demonstrated that caffeic or ferulic acids effectively decreased melanin synthesis in the B16 melanoma cells (27.4% and 24.4%, respectively) by a different mechanism of action. Ferulic acid is directly bound to the tyrosinase active site, whereas complex caffeic acid and tyrosinase showed no direct binding. It was supported by ferulic acid (51.5 μM) suppressed 98.2% conversion of tyrosine to DOPA and 45.5 % dopaquinone formation from DOPA. However, caffeic acid (55.5 μM) only inhibited 15.7% of the formation of DOPA and 22.3% of dopaquinone. Ferulic acid is estimated to be more active than caffeic acid due to the presence of an electron-donating methoxy group, which increases the radical's stabilization through electron delocalization after hydrogen donation by the hydroxyl group [54].

Furthermore, ferulic acid has a conjugated double-bond side chain alkyl, contributing to its more potent antioxidant ability. Also, the ferulic acid's COOH group can interact with Cu^{2+} and Fe^{2+} ions. Therefore, the type of inhibition mechanism for ferulic acid is competitive inhibition [26].

3.5. Combination of polyphenols as tyrosinase inhibitors

Yu et al. (2021) [37] performed an experimental study about the combination effect between ferulic

acid and 4-hydroxycinnamic acid. When they bind to the active tyrosinase cavity, their hydroxyl groups could combine with amino acid residues in the enzyme to form hydrogen bonding. Their complex was found to more effectively inhibit tyrosinase activity (inhibition rate of 90.44%) than employing ferulic acid and 4-hydroxycinnamic acid alone (inhibition rate of 22.17 and 12.15 % respectively). It shows that the dominant factor impacting tyrosinase activity's inhibitory capacity is the binding of individual polyphenols tyrosinase and their structure and molecular weight [36].

Then, Yu et al. (2019) [38] reported that combinations of different polyphenol concentrations were employed to reveal the synergistic effect. The mixture of quercetin, ferulic acid, and cinnamic acid (KI = 0.239 mM) was proven to have a higher inhibition ability than quercetin (KI = 0.361 mM). Its complex is more stable and supported by the hydrophobic effect, the primary driving force during the binding process. Thermodynamically, the addition of cinnamic acid and ferulic acid promotes spontaneous binding with lower free binding energy. Moreover, adding ferulic acid can destroy the secondary structure of the proteins and hydrogen networks [38].

3.6. Physicochemical Properties of Ferulic Acid Derivatives Mentioned in this Review.

Antioxidants' affinity for lipid substrates and their capacity to scavenge free radicals may play significant roles in the activity of phenol compounds. Compound affinity with lipid substrates is referred to as the log P value. The partition coefficient indicates the concentration of solute in the organic and aqueous phases. A positive value of Log P denotes a higher concentration in the lipid or more affinity with the lipid phase related to bioavailability [55]. Therefore, it has been used to determine solubility and is crucial for predicting general toxicity.

The essential physiochemical properties of drug molecules responsible for their penetration are drug molecule size, molecular weight, lipophilicity, hydrogen-bonding groups, solubility, ionization of drug molecules, stereochemistry, and steric interaction [56]. Generally, molecules should have a molecular weight under 500 Dalton [57], a low partition coefficient [58], a minimum PSA [59], and several hydrogen-bonding groups [60] to increase the permeability through the skin. **Table 4** shows the essential physicochemical properties of the most promising molecules mentioned in this article, computed using the open-source software Molinspiration.

Based on the software calculations, the reported derivatives displayed a molecular weight in the range of 206.24–452.55; a calculated Log P in the range of 0.53–4.19; a tPSA in the range of 46.53–117.12; several donor hydrogen bonding in the range 1-4; and an acceptor hydrogen bonding in the range 3–8. These results indicate that these derivatives will likely penetrate the skin and can be considered for further new drugs or cosmetic optimization.

Table 4. The properties of ferulic acid derivatives are mentioned in the review.

No Structure	Molecular Weight	LogP	TPSA	Hydrogen Bonding		Ref.
				donor	acceptor	
1	297.35	2.91	58.56	2	4	[12]
2	313.35	2.43	78.79	3	5	[12]
3	329.35	1.95	99.02	4	6	[12]
4	351.41	2.56	77.03	2	6	[12]
5	369.42	3.14	84.86	2	6	[29]
6	356.38	1.69	107.89	4	7	[30]
7	306.32	0.53	99.10	3	7	[30]
8	412.42	3.05	100.66	3	7	[31]
9	373.38	2.90	84.86	2	6	[31]
10	382.46	2.70	62.24	1	6	[32]
11	370.42	2.81	53.01	1	5	[32]
12	206.24	2.05	46.53	1	3	[33]
13	293.32	1.68	84.86	2	6	[34]
14	321.27	2.46	84.86	2	6	[34]
15	335.40	2.99	84.86	2	6	[34]
16	335.36	1.48	90.94	1	7	[34]
17	363.41	2.26	90.94	1	7	[34]
18	377.44	2.79	90.94	1	7	[34]
19	236.22	1.05	72.84	1	5	[34]
20	412.44	1.91	117.12	4	8	[35]
21	440.5	2.48	106.13	3	8	[35]
22	452.55	4.19	89.06	3	7	[35]
23	386.40	3.63	102.3	2	7	[36]
24	412.22	3.54	99.14	1	7	[36]

4. Conclusions

The present work explored the potential of ferulic acid and its synthetic derivatives as anti-tyrosinase. The ferulic acid's anti-tyrosinase capacity is due to the presence of double bond conjugation as a side chain in its molecule. Additionally, the substituents on the phenyl ring improved the inhibitory effects on monophenolase activity. The halogen substituent in the 4-position of the phenyl ring enhanced the anti-tyrosinase activity. Variations in the substituent pattern and the chain length that separate the phenyl ring and the amide linkage can change the inhibitory

activity. A combination of ferulic acid and other cinnamic acid derivatives could be beneficial in generating a more stable complex.

Conflicts of interest

There are no conflicts to declare.

References

[1] G. Karakaya, A. Türe, A. Ercan, S. Öncül, and M. D. Aytemir, "Synthesis, computational molecular docking analysis and effectiveness on tyrosinase inhibition of kojic acid derivatives," *Bioorg Chem*, vol. 88, Jul. 2019, doi: 10.1016/j.bioorg.2019.102950.

[2] A. M. Muddathir, K. Yamauchi, I. Batubara, E. A. M. Mohieldin, and T. Mitsunaga, "Anti-tyrosinase, total phenolic content and antioxidant activity of selected Sudanese medicinal plants," *South African Journal of Botany*, vol. 109, pp. 9–15, Mar. 2017, doi: 10.1016/j.sajb.2016.12.013.

[3] W. Cao *et al.*, "Unraveling the structure and function of melanin through synthesis," *J Am Chem Soc*, vol. 143, no. 7, pp. 2622–2637, Feb. 2021, doi: 10.1021/jacs.0c12322.

[4] T. Pillaiyar, M. Manickam, and V. Namasivayam, "Skin whitening agents: Medicinal chemistry perspective of tyrosinase inhibitors," *Journal of Enzyme Inhibition and Medicinal Chemistry*, vol. 32, no. 1. Taylor and Francis Ltd, pp. 403–425, 2017. doi: 10.1080/14756366.2016.1256882.

[5] D. Feng, Z. Fang, and P. Zhang, "The melanin inhibitory effect of plants and phytochemicals: A systematic review," *Phytomedicine*, vol. 107. Elsevier GmbH, Dec. 01, 2022. doi: 10.1016/j.phymed.2022.154449.

[6] K. Zduńska, A. Dana, A. Kolodziejczak, and H. Rotsztejn, "Antioxidant properties of ferulic acid and its possible application," *Skin Pharmacology and Physiology*, vol. 31, no. 6. S. Karger AG, pp. 332–336, Oct. 01, 2018. doi: 10.1159/000491755.

[7] T. Shojazadeh *et al.*, "New insights into the inhibitory effect of phenol carboxylic acid antioxidants on mushroom tyrosinase by molecular dynamic studies and experimental assessment," *J Biomol Struct Dyn*, 2023, doi: 10.1080/07391102.2023.2175038.

[8] R. Batista, "Uses and Potential Applications of Ferulic Acid," warren Bryce, Ed., 1st ed.New York: Nova Science Publishers, Inc., 2014, pp. 39–70. [Online]. Available: https://www.researchgate.net/publication/266201761

[9] Y. Z. Zheng, G. Deng, and Y. C. Zhang, "Multiple free radical scavenging reactions of flavonoids," *Dyes and Pigments*, vol. 198, Feb. 2022, doi: 10.1016/j.dyepig.2021.109877.

[10] K. Pei, J. Ou, C. Huang, and S. Ou, "Derivatives of Ferulic Acid: Structure, Preparation and Biological Activities," *Annu Res Rev Biol*, vol. 5, no. 6, pp. 512–528, Jan. 2015, doi: 10.9734/arrb/2015/14104.

[11] M. J. Page *et al.*, "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews," *The BMJ*, vol. 372. BMJ Publishing Group, Mar. 29, 2021. doi: 10.1136/bmj.n71.

[12] S. Okombi, D. Rival, S. Bonnet, A. M. Mariotte, E. Perrier, and A. Boumendjel, "Analogues of N-hydroxycinnamoylphenalkylamides as inhibitors of human melanocyte-tyrosinase," *Bioorg Med Chem Lett*, vol. 16, no. 8, pp. 2252–2255, Apr. 2006, doi: 10.1016/j.bmcl.2006.01.022.

[13] A. Chaiprasongsuk, T. Onkoksoong, T. Pluemsamran, S. Limsaengurai, and U. Panich, "Photoprotection by dietary phenolics against melanogenesis induced by UVA through Nrf2-dependent antioxidant responses," *Redox Biol*, vol. 8, pp. 79–90, Aug. 2016, doi: 10.1016/j.redox.2015.12.006.

[14] H. Maruyama, F. Kawakami, T.-T. Lwin, M. Imai, and F. Shamsa, "Biochemical Characterization of Ferulic Acid and Caffeic Acid Which Effectively Inhibit Melanin Synthesis via Different Mechanisms in B16 Melanoma Cells," 2018.

[15] J. Chen, M. Ran, M. Wang, X. Liu, S. Liu, and Y. Yu, "Structure-activity relationships of antityrosinase and antioxidant activities of cinnamic acid and its derivatives," *Biosci Biotechnol Biochem*, vol. 85, no. 7, pp. 1697–1705, Jul. 2021, doi: 10.1093/bbb/zbab084.

[16] A. V. Phadke, A. A. Tayade, and M. P. Khambete, "Therapeutic potential of ferulic acid and its derivatives in Alzheimer's disease—A systematic review," *Chemical Biology and Drug Design*, vol. 98, no. 5. John Wiley and Sons Inc, pp. 713–721, Nov. 01, 2021. doi: 10.1111/cbdd.13922.

[17] E. Graf, "Antioxidant potential of ferulic aci," *Free Radic Biol Med*, pp. 453–448, 1992.

[18] S. Ou and K. C. Kwok, "Ferulic acid: Pharmaceutical functions, preparation and applications in foods," *Journal of the Science of Food and Agriculture*, vol. 84, no. 11. pp. 1261–1269, Aug. 30, 2004. doi: 10.1002/jsfa.1873.

[19] C. Peyrot, A. A. M. Peru, L. M. M. Mouterde, and F. Allais, "Proline-Mediated Knoevenagel-Doebner Condensation in Ethanol: A Sustainable Access to p-Hydroxycinnamic Acids," *ACS Sustain Chem Eng*, vol. 7, no. 10, pp. 9422–9427, May 2019, doi: 10.1021/acssuschemeng.9b00624.

[20] L. M. M. Mouterde and F. Allais, "Microwave-Assisted Knoevenagel-Doebner Reaction: An Efficient Method for Naturally Occurring Phenolic Acids Synthesis," *Front Chem*, vol. 6, Sep. 2018, doi: 10.3389/fchem.2018.00426.

[21] R. Widyowati, "Synthesis of Ferulic Acid and Its Non Covalent Inclusion with Hydroxypropyl-b-Cyclodextrin."

[22] D. C. Marcato, C. M. Spagnol, H. R. N. Salgado, V. L. B. Isaac, and M. A. Corrêa, "New and potential properties, characteristics, and analytical methods of ferulic acid: A review," *Brazilian Journal of Pharmaceutical Sciences*, vol. 58, 2022, doi: 10.1590/s2175-97902020000118747.

[23] Y. T. Sohn and J. H. Oh, "~rc!~ibr~ of barrnacal ~e~earcb Characterization of Physicochemical Properties of Ferulic Acid," 2003. [Online]. Available: http://apr.psk.or.kr

[24] Z. Zhao and M. H. Moghadasian, "Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: A review," *Food Chemistry*, vol. 109, no. 4. pp. 691–702, Aug. 15, 2008. doi: 10.1016/j.foodchem.2008.02.039.

[25] N. Kumar and V. Pruthi, "Potential applications of ferulic acid from natural sources," *Biotechnology Reports*, vol. 4, no. 1. Elsevier B.V., pp. 86–93, Dec. 01, 2014. doi: 10.1016/j.btre.2014.09.002.

[26] D. Shukla *et al.*, "Ferulic acid-loaded drug delivery systems for biomedical applications," *Journal of Drug Delivery Science and Technology*, vol. 75. Editions de Sante, Sep. 01, 2022. doi: 10.1016/j.jddst.2022.103621.

[27] M. Srinivasan, A. R. Sudheer, and V. P. Menon, "Serial Review Ferulic Acid: Therapeutic Potential Through Its Antioxidant Property," 2007.

[28] A. Mancuso, M. C. Cristiano, R. Pandolfo, M. Greco, M. Fresta, and D. Paolino, "Improvement of Ferulic Acid Antioxidant Activity by Multiple Emulsions: In Vitro and In Vivo Evaluation," *Nanomaterials*, vol. 11, no. 2, pp. 1–16, Feb. 2021, doi: 10.3390/nano11020425.

[29] Q. Fan *et al.*, "Tyrosinase inhibitory effects and antioxidative activities of novel cinnamoyl amides with amino acid ester moiety," *Food Chem*, vol. 134, no. 2, pp. 1081–1087, Sep. 2012, doi: 10.1016/j.foodchem.2012.03.021.

[30] S. Y. Kwak, J. K. Yang, H. R. Choi, K. C. Park, Y. B. Kim, and Y. S. Lee, "Synthesis and dual biological effects of hydroxycinnamoyl phenylalanyl/prolyl hydroxamic acid derivatives as tyrosinase inhibitor and antioxidant," *Bioorg Med Chem Lett*, vol. 23, no. 4, pp. 1136–1142, Feb. 2013, doi: 10.1016/j.bmcl.2012.10.107.

[31] M. Chochkova *et al.*, "N-Hydroxycinnamoyl amides of fluorinated amino acids: Synthesis, anti-tyrosinase and DPPH scavenging activities," *J Fluor Chem*, vol. 156, pp. 203–208, 2013, doi: 10.1016/j.jfluchem.2013.09.013.

[32] Z. T. Gur, S. shefkeh, and L. Orhan, "Novel piperazine amides of cinnamic acid _ derivatives as tyrosinase inhibitors," *Lett. Drug Des. Discov*, vol. 16, pp. 36–44, 2019.

[33] Y. Bai, J. Jian, D. Liu, and X. Zhao, "Synthesis, characterization and application of a new biomass-based antioxidant derived from vanillin and methyl ethyl ketone," *J Clean Prod*, vol. 316, Sep. 2021, doi: 10.1016/j.jclepro.2021.128315.

[34] D. Wang, J. Zhu, J. R. Xu, and D. D. Ji, "Synthesis of N-hydroxycinnamoyl amide derivatives and evaluation of their anti-oxidative and anti-tyrosinase activities," *Bioorg Med Chem*, vol. 27, no. 20, Oct. 2019, doi: 10.1016/j.bmc.2019.05.031.

[35] J. hoon Ha and S. N. Park, "Dimeric cinnamoylamide analogues for regulation of tyrosinase activity in melanoma cells: A role of diamide-link chain length," *Bioorg Med Chem*, vol. 26, no. 23–24, pp. 6015–6022, Dec. 2018, doi: 10.1016/j.bmc.2018.10.036.

[36] K. Tang *et al.*, "Design, synthesis of Cinnamyl-paeonol derivatives with 1, 3-Dioxypropyl as link arm and screening of tyrosinase inhibition activity in vitro," *Bioorg Chem*, vol. 106, Jan. 2021, doi: 10.1016/j.bioorg.2020.104512.

[37] Q. Yu and L. Fan, "Understanding the combined effect and inhibition mechanism of 4-hydroxycinnamic acid and ferulic acid as tyrosinase inhibitors," *Food Chem*, vol. 352, Aug. 2021, doi: 10.1016/j.foodchem.2021.129369.

[38] Q. Yu, L. Fan, and Z. Duan, "Five individual polyphenols as tyrosinase inhibitors: Inhibitory activity, synergistic effect, action mechanism, and molecular docking," *Food*

Chem, vol. 297, Nov. 2019, doi: 10.1016/j.foodchem.2019.05.184.

[39] S. Zolghadri *et al.*, "A comprehensive review on tyrosinase inhibitors," *Journal of Enzyme Inhibition and Medicinal Chemistry*, vol. 34, no. 1. Taylor and Francis Ltd, pp. 279–309, Jan. 01, 2019. doi: 10.1080/14756366.2018.1545767.

[40] S. Athar Ali, "Biochemical aspects of mammalian melanocytes and the emerging role of melanocyte stem cells in dermatological therapies," 2018. [Online]. Available: https://www.researchgate.net/publication/322592409

[41] M. A. Maranduca *et al.*, "Synthesis and physiological implications of melanic pigments (review)," *Oncol Lett*, vol. 17, no. 5, pp. 4183–4187, May 2019, doi: 10.3892/ol.2019.10071.

[42] J. D'Orazio, S. Jarrett, A. Amaro-Ortiz, and T. Scott, "UV radiation and the skin," *International Journal of Molecular Sciences*, vol. 14, no. 6. MDPI AG, pp. 12222–12248, 2013. doi: 10.3390/ijms140612222.

[43] S. Ito, S. Del Bino, T. Hirobe, and K. Wakamatsu, "Improved hplc conditions to determine eumelanin and pheomelanin contents in biological samples using an ion pair reagent," *Int J Mol Sci*, vol. 21, no. 14, pp. 1–12, Jul. 2020, doi: 10.3390/ijms21145134.

[44] S. Ito, N. Suzuki, S. Takebayashi, S. Commo, and K. Wakamatsu, "Neutral pH and copper ions promote eumelanogenesis after the dopachrome stage," *Pigment Cell Melanoma Res*, vol. 26, no. 6, pp. 817–825, Nov. 2013, doi: 10.1111/pcmr.12137.

[45] K. Wakamatsu, J. H. Zippin, and S. Ito, "Chemical and biochemical control of skin pigmentation with special emphasis on mixed melanogenesis," *Pigment Cell and Melanoma Research*, vol. 34, no. 4. John Wiley and Sons Inc, pp. 730–747, Jul. 01, 2021. doi: 10.1111/pcmr.12970.

[46] A. Palurnbo, M. D'ischia, G. Misuraca, and G. Prota, "Effect of metal ions on the rearrangement of dopachrome," 1987.

[47] Z. Peng *et al.*, "A systematic review of synthetic tyrosinase inhibitors and their structure-activity relationship," *Critical Reviews in Food Science and Nutrition*, vol. 62, no. 15. Taylor and Francis Ltd., pp. 4053–4094, 2022. doi: 10.1080/10408398.2021.1871724.

[48] N. Rangkadilok, S. Sitthimonchai, L. Worasuttayangkurn, C. Mahidol, M. Ruchirawat, and J. Satayavivad, "Evaluation of free radical scavenging and antityrosinase activities of standardized longan fruit extract," *Food and Chemical Toxicology*, vol. 45, no. 2, pp. 328–336, Feb. 2007, doi: 10.1016/j.fct.2006.08.022.

[49] T. H. Chou, H. Y. Ding, W. J. Hung, and C. H. Liang, "Antioxidative characteristics and inhibition of α-melanocyte-stimulating hormone-stimulated melanogenesis of vanillin and vanillic acid from Origanum vulgare," *Exp Dermatol*, vol. 19, no. 8, pp. 742–750, Aug. 2010, doi: 10.1111/j.1600-0625.2010.01091.x.

[50] F. Sioud, M. Maatouk, I. M. Bzeouich, L. C. Ghedira, and S. Kilani-Jaziri, "In vitro anti-melanoma effect of polyphenolic compounds," *Asian Pac J Trop Biomed*, vol. 12, no. 10, pp. 446–452, Oct. 2022, doi: 10.4103/2221-1691.357744.

[51] R. Romagnoli *et al.*, "Cinnamic acid derivatives linked to arylpiperazines as novel potent inhibitors of tyrosinase activity and melanin synthesis," *Eur J Med Chem*, vol. 231, Mar. 2022, doi: 10.1016/j.ejmech.2022.114147.

[52] S. Das and A. B. H. Wong, "Stabilization of ferulic acid in topical gel formulation via nanoencapsulation and pH optimization," *Sci Rep*, vol. 10, no. 1, Dec. 2020, doi: 10.1038/s41598-020-68732-6.

[53] M. A. Dettori *et al.*, "Synthesis and studies of the inhibitory effect of hydroxylated phenylpropanoids and biphenols derivatives on tyrosinase and laccase enzymes," *Molecules*, vol. 25, no. 11, Jun. 2020, doi: 10.3390/molecules25112709.

[54] M. Karamac, L. Koleva, V. D. Kancheva, and R. Amarowicz, "The structure-antioxidant activity relationship of ferulates," *Molecules*, vol. 22, no. 4, Apr. 2017, doi: 10.3390/molecules22040527.

[55] J. Plante and S. Werner, "JPlogP: An improved logP predictor trained using predicted data," *J Cheminform*, vol. 10, no. 1, Dec. 2018, doi: 10.1186/s13321-018-0316-5.

[56] S. Supe and P. Takudage, "Methods for evaluating penetration of drug into the skin: A review," *Skin Research and Technology*, vol. 27, no. 3. John Wiley and Sons Inc, pp. 299–308, May 01, 2021. doi: 10.1111/srt.12968.

[57] J. D. Bos and M. M. H. M. Meinardi, "EXPERIMENTAL DERMATOLOGY The 500 Dalton rule for the skin penetration of chemical compounds and drugs Bos JD, Meinardi MMHM. The 500 Dalton rule for the skin penetration," *Exp Dermatol*, vol. 9,

pp. 165–169, 2000, [Online]. Available: http://chemfinder.

[58] B. J. Bennion *et al.*, "Predicting a Drug's Membrane Permeability: A Computational Model Validated with in Vitro Permeability Assay Data," *Journal of Physical Chemistry B*, vol. 121, no. 20, pp. 5228–5237, May 2017, doi: 10.1021/acs.jpcb.7b02914.

[59] M. Janicka, A. Mycka, M. Sztanke, and K. Sztanke, "Predicting pharmacokinetic properties of potential anticancer agents via their chromatographic behavior on different reversed phase materials," *Int J Mol Sci*, vol. 22, no. 8, Apr. 2021, doi: 10.3390/ijms22084257.

[60] M. S. Roberts, W. J. Pugh, and J. Hadgraft, "international journal of pharmaceutics Epidermal permeability: penetrant structure relationships. 2. The effect of H-bonding groups in penetrants on their diffusion through the stratum corneum," 1996.